Review article

J. Perinat. Med.
2 (1974) 147

Intrauterine growth retardation. A new systematic approach based on the clinical and biochemical characteristics of this condition

P. Rosso, M. Winick

Department of Pediatrics and Institute of Human Nutrition, College of Physicians and Surgeons of Columbia University, New York

It took a decade after the pioneering observations on prematurity made in 1936 [36] and 1967 [30], for us to realize that not all low birth weight infants are premature. Certain infants are of low birth weight for their gestational age regardless of whether they are born prematurely, at term, or even post term. We call these infants by a variety of names [30, 17, 45, 46, 51], the most common being intrauterine growth retarded [52], small-for-dates [8], small for gestational age [3] and intrauterine malnourished [43]. These names however, are simply descriptive and in no way clarify the etiology of the growth failure. The assumption has always been made that the major cause of this syndrome was "placental insufficiency" [17, 46, 3]. However the term "placental insufficiency" is itself vague, never actually having been defined either morphologically, physiologically or biochemically. No doubt this terminology has been partly responsible for our characterization of these infants into a single syndrome. **Recently we have begun to realize that low birth weight for gestational age does not define a single syndrome.** Just as all babies under 2.500 gms are not premature but constitute a heterogeneous group, so all "small for dates" babies are not a single entity; they too are a heterogeneous group.

In this paper we would like to discuss some of the current concepts related to fetal growth retardation and to present new evidence supporting the position that there are different types of infants with intrauterine growth retardation and that these different types can and should be recognized.

Curriculum vitae

PEDRO ROSSO *was born in Italy in 1941 and went to school in Santiago, Chile. He entered the Catholic University in Santiago in 1959 and he was qualified as a physician in 1966 by the University of Chile. He served as a Resident in Pediatrics at the Hospital Roberto del Rio, University of Chile, from 1966 to 1969. He continued his post-graduate training at Cornell University Medical College in 1970 where he spent two years as a fellow in the Division of Growth and Development of the Department of Pediatrics. During his fellowship he began to study the effects of nutrition on the control mechanisms of prenatal and postnatal growth and has since worked in this area. In 1973 he was appointed Assistant Professor of Pediatrics, College of Physicians and Surgeons, Columbia University. Current studies deal with maternal nutrition and placental transfer of nutrients.*

1 Etiological classification of intrauterine growth retardation

At present intrauterine growth retardation (IUGR) is defined as a birth weight below the 10th percentile for a given gestational age [3]. This definition however, characterizes a variety of different conditions. Although all of these conditions ultimately affect fetal growth, **some may be "intrinsic" to the fetus or placenta and others may be caused by "extrinsic" factors acting directly on the fetus, both the fetus and the placenta or the placenta primarily and the fetus only secondarily.** We believe that the various entities comprising

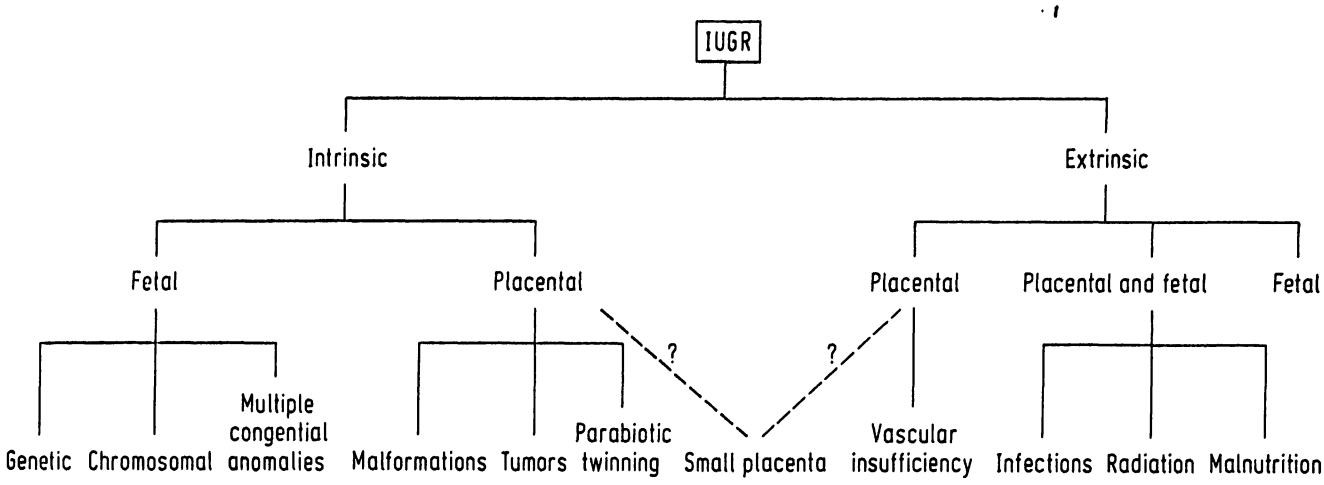

Fig. 1. Etiological classification of intrauterine growth retardation (IUGR).

IUGR can be classified within this broad characterization. Fig. 1 presents our theoretical model for the classification of IUGR.

1.1 Intrinsic causes of IUGR

1.1.1 Fetal

The "intrinsic" fetal causes of IUGR are due to genetic factors, chromosomal abnormalities or faulty differentiation during organogenesis. Evidence for genetic variations comes from observation of human populations and from studies in experimental animals. In a study of all babies born in Baltimore from 1959 through 1961 with an estimated gestational age of thirty-six to thirty-seven weeks, approximately fifteen per cent weighed 2000 gms or less [4]. This weight is below the 10th percentile of the Lubchenko curve [29] for babies of this age and consequently these infants could be considered small-for-dates. Similar variations in body weight have been described in newborn rhesus monkeys bred in captivity [15]. Here the gestational age can be carefully calculated and prematures not inadvertently counted. **It is impossible to know the relative contributions of genetic variability and environmental stresses in accounting for this wide range of birth weights.** However some of these cases can be assumed to be genetically small rather than growth retarded.

Chromosomal alterations of many different varieties result in IUGR. Trisomy 18 [37] and Turner's syndrome (45/XO) [39] are commonly associated with a marked reduction in birth weight. In addition many other congenital anomalies without chromosomal alterations are also associated with IUGR. This relationship of multiple congenital anomalies and marked growth failure is especially noticeable when the skeleton or the central nervous system is involved [48].

1.1.2 Placental

A number of the "intrinsic" placental changes which have been associated with IUGR have been recently reviewed [44]. These include a number of rare malformations of the placenta such as velamentous and battledore cord insertions and vascular tumors of the placenta and cord. In addition vascular transfusion in monochorial twin placentas can be included in this group.

1.2 Extrinsic causes of IUGR

1.2.1 Fetal

At this time, although they undoubtedly exist, we are unable to identify with certainty any external agents which affect only the fetus and not the placenta which are associated with IUGR, although certain teratogenic agents may fall into this category.

1.2.2 Feto-placental

A variety of external stimuli will produce IUGR by affecting both the placenta and the fetus. Thus the fetus fails to grow not only as a consequence of being directly affected by the agent but also as a consequence of placental involvement. A

classic example of this type of IUGR is **rubella infection.** Data collected during the 1963—1964 rubella epidemic in the U. S. demonstrated that in a group of 58 infants with congenital rubella, 60 per cent were below the 10th percentile for body weight [10]. Analysis of the placentas from cases of congenital rubella, often demonstrate villous placentitis and viral damage to the vascular endothelium [12]. These findings are consistent with the interpretation that placental blood circulation and subsequent function was impaired.

Compared to rubella, information is scarce relating **cytomegalovirus infection** to IUGR. However in a recent study seven out of twenty infants with cytomegalovirus infection showed marked growth retardation [31]. No correlation was made between the cases of IUGR and any placental pathology.

Low birth weight has also been associated with **other viral infections** such as herpes simplex, and with **parasitic infections** such as malaria and toxoplasmosis. In a number of these infections however it is difficult to distinguish from available reports between prematurity and IUGR [22].

Another environmental hazard, **ionizing radiation** is known to cause severe growth retardation associated with severe central nervous system damage. However, whether or not the placena ist also affected and hence classification in this category is warranted is not well documented [63].

Perhaps the most common cause of IUGR in this category is **poor nutrition of the mother.** While we may still debate whether mild dietary restriction will result in clinically recognizable intrauterine growth retardation certainly severe famines are associated with a high incidence of low birth weight babies [5]. In addition, recent studies in Guatemala have clearly demonstrated an increase in about 400 gms in the birth weight of infants from mothers with subclinical protein calorie malnutrition when these women are adequately supplemented with either calories or protein [18]. Thus fetal growth is retarded in underprivileged segments of developing countries and perhaps under these conditions the fetus may become more "sensitive" to the effects of other growth retarding stimuli. It is possible that the higher incidence of IUGR in low income groups throughout the world [16] can be explained on this basis.

The mechanisms by which maternal malnutrition retards fetal growth are poorly understood. HAMMOND has theorized that, because of the higher metabolic rate of its tissues, the fetus would be able to compete successfully with the mother for available nutrients [19]. According to this theory fetal growth would be retarded only after extreme maternal depletion. HAMMOND, however, considered the placenta merely as a passive screen. Recent data have demonstrated that maternal undernutrition induces profound changes in placenta. DNA content is reduced [54, 11] both the villous mass and surface area are reduced [24] and the proportion of free ribosomes to polysomes are increased [25]. All these changes demonstrate that placenta like any other rapidly growing organ is highly susceptible to the effects of malnutrition [55]. The functional implications of these placental changes are still unknown. However at least one hormonal function, estriol secretion, is retarded by maternal malnutrition [23].

1.2.3 Placental

The placenta represents practically the only link between the fetus and the mother. It is wholly responsible for transporting nutrients to and removing waste products from the fetus. In addition, hormones secreted by the placenta are responsible for some of the physiologic changes of pregnancy which occur in the mother. By inducing these changes the placenta may indirectly influence its own growth and the growth of the fetus. Thus any external stimulus impeding placental function may impede fetal growth in a variety of ways.

The most common external factors affecting the placenta all seem to retard utero-placental blood flow. Just how this comes about and the precise pathophysiology is still unknown. However the fact that there is a higher incidence of vascular lesions found in placentas from

growth retarded infants strongly suggests some type of "vascular insufficiency" mechanism [17, 43]. Some of these lesions such as pale areas, large areas of ischemic necrosis of villi and infarcts are also seen in placentas from normal newborns, indicating that the lesions are nonspecific [43]. **Thus it is the extent of the damage and not the type of lesion which determines whether fetal growth failure will ensue.** Other maternal conditions in which vascular lesions of the placenta are likely to develop are essential hypertension and collagen vascular disease. More data from good clinical studies are needed to characterize the extent and type of the lesions in these conditions. Another piece of evidence suggesting a vascular effect is the clear relationship between toxemia and IUGR [33].

1.2.4 Conditions not yet classifiable

Maternal smoking during pregnancy is strongly associated with IUGR [41]. Several explanations for this association have been offered. These include carbon monoxide effects, reduced placental blood flow due to pharmacologic agents and reduction in maternal food intake [27]. Thus smoking may act either by affecting the placenta alone or by affecting the feto-placental unit. Perhaps the most difficult type of IUGR to classify is the **small infant with a small placenta.** In infants falling within the normal range of birth weights there is a direct correlation between fetal weight and placental weight [1]. Therefore it might appear logical that abnormally small fetuses would have abnormally small placentas. However this is not always true. In a recent study only 26 placentas from a group of 50 babies with "placental insufficiency" and intrauterine growth failure had a weight below the 10th percentile [43]. Thus at least **one half of these children had a disproportionally large placenta for their body weight.** In addition there are isolated case reports supporting this disproportional relationship. For example, there is the case of an infant born at 38 weeks of gestation weighing 1885 g. The placenta was scarred and showed extensive infarctions but weighed 590 g [17]. This inconsistency in the relative placental to fetal weight in IUGR may explain the inconsistency in the data which compares fetal body weight/placental weight ratios in normal infants with those in growth retarded infants. Some studies describe an elevated ratio [42, 62] whereas in other studies the ratio was normal [64]. Attempts to further characterize the small and large placentas from IUGR have not been made.

From the data above, it should be apparent that IUGR has multiple causes, some intrinsic to the growing fetus or placenta and others imposed on them from the outside environment. Recently we are also finding out, that clinically all cases of IUGR do not look alike. Separation of these infants into the proper clinical type often allows us to classify them into the proper etiologic category and in addition may give us valuable clues to both prognosis and therapy.

2 Clinical types of IUGR

Clinically, growth retarded neonates can be separated into **two large groups. Those with obvious congenital malformations and those without.** The separation into the proper group is quite simple and depends entirely on a careful physical examination. These two major groups can be further subdivided into a clinical classification as seen in Fig. 2.

2.1 Infants with multiple congenital anomalies

The etiology of the growth failure as well as of the malformations may be either "intrinsic" or "extrinsic" to the fetus and placenta. In all of these infants the growth failure is a secondary symptom. The type of growth failure seen is variable. The relative growth of the head to the rest of the body differs with different types of anomalies. For example, babies with Down's syndrome have a reduced head circumference/body length ratio [28]. The infants with multiple birth defects can be recognized at birth by the type of malformation or by the signs and symptoms of the disease entity causing the malformations. In the infants with "intrinsic" growth failure the problem seems to involve only the fetus, the placenta appearing normal. A study

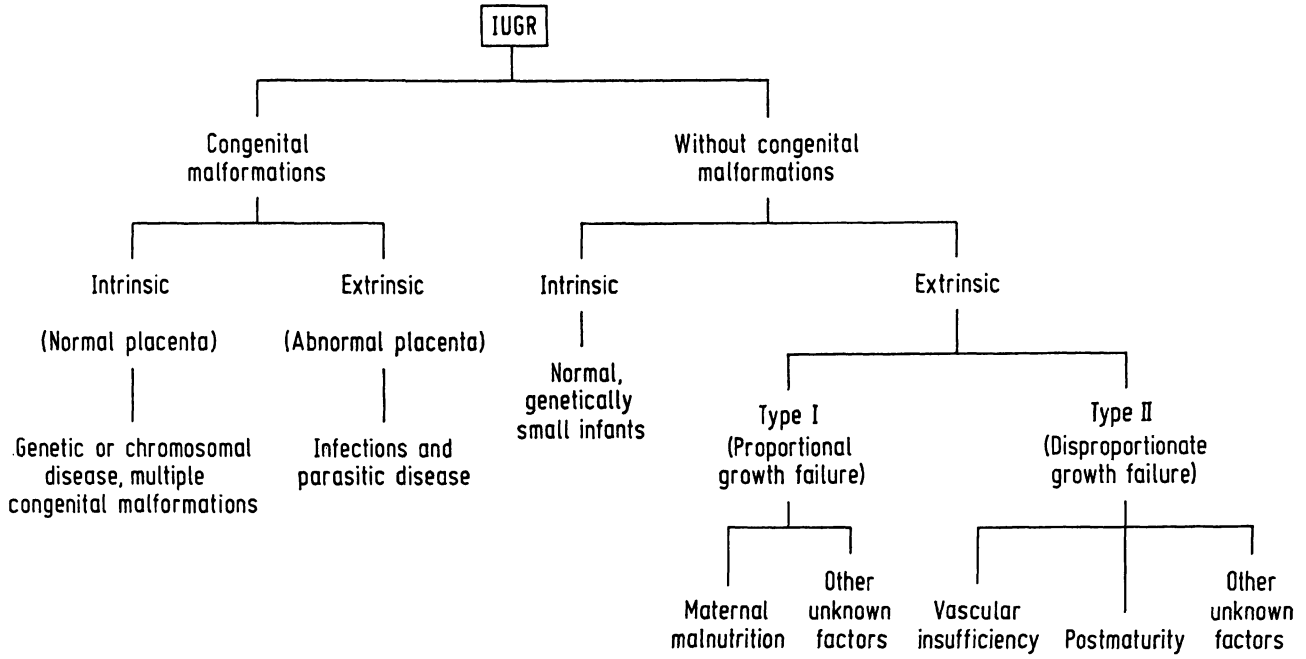

Fig. 2. Clinical classification of intrauterine growth retardation (IUGR).

examining placenta in these cases has revealed that placental weight, cell number (DNA content) and protein and RNA per cell were all normal [56]. By contrast in infants whose growth failure is caused by extrinsic factors, generally intrauterine infections, considerable placental pathology can be found. For example, as previously mentioned in cases of congenital rubella villous changes and changes in the vascular endothelium are prominent [12].

2.2 Infants without congenital anomalies

It is these infants again referred to in, the literature as "intrauterine malnourished" [30, 34, 42], who constitute the major problem to the clinician as far as diagnosis, prognosis and therapy is concerned. Except for those falling into the genetically small group all of these infants are growth retarded by virtue of external forces working on either the placenta or the fetoplacental unit. The **genetically small infants** can be diagnosed by exclusion, by their normal proportions and by the size of their parents and other close relatives [49]. **They always fall between the 10th and 3rd percentile of weight for gestational age.** In the great majority of the infants in this category external "stresses" have resulted in retardation of normal growth. **Clinically these infants can be divided into two types depending on the relative growth of the head and body length to the rest of the organs of the body** [7]. **Type I** is a small infant with a **proportionally** small head and reduced body length and body weight. **Type II** is a small infant whose head and length is relatively normal size for the gestational age and whose **weight/length ratio is reduced** [47]. Although these two types are relatively easy to distinguish when they occur in the pure form it is conceivable that a considerable amount of overlap may be present. We will examine the evidence demonstrating the existence of these two clinical types and some of their most likely etiologies and then attempt to classify a number of infants who may fall into either category.

2.2.1 Type I IUGR

Clinically these infants appear small, normally **proportioned** and remind one of the infant who is suffering from a mild postnatal caloric deprivation [9] (Fig. 3). This type of growth failure has been produced in **experimental animals by restricting the protein or calorie intake of the mother** [57]. Under these con-

Fig. 3. Infant born at 36 weeks of gestation weighing 860 g showing clincal characteristics of IUGR Type I.

ditions biochemical and cellular changes are induced in both the placenta and fetal organs early in gestation. For example reduction in the activity of DNA polymerase, a change characteristic of postnatal malnutrition, is present in placentas from malnourished dams [6]. In addition cell division is retarded in placental and fetal organs. **Fetal brain shows about a 15 to 20% reduction in cell number.** Other organs of the fetus show retarded cell division to approximately the same degree as brain so that liver and other organs also have 15—20% fewer cells [57]. Thus we have proportional growth failure; **all organs retarded to approximately the same extent.** If the malnutrition is continued postnatally for the first twenty one days of **the** (thus malnutrition has been present throughout the entire period when brain cells are dividing), there is a 60% reduction in brain cell number by the time the animal is weaned [60]. It would appear that undernutrition imposed throughout gestation and lactation has an effect which is more than additive.

Does the **human counterpart** of this situation exist? More and more evidence is suggesting that it does. A recent report in which 1.044 consecutive autopsies of well preserved stillborn and newborn infants in New York City were analyzed indicates a **clear correlation between fetal growth and maternal nutrition** [35]. This study demonstrates that mothers who were underweight before pregnancy and had a very low gestational weight gain, and whose dietary intake of protein and calories was poor, delivered small babies. The subsequent analysis of the fetal organs demonstrated a 13 per cent reduction of brain weight and a similar reduction for other organs including placenta: a picture analogous to the effects of maternal dietary restriction in the rat (Tab. I).

Tab. I. Effect of maternal malnutrition on fetal growth and the growth of several organs in rats and humans at 21 and over 33 weeks of gestation respectively; values are expressed as percent of normals.

	Rat*	Human [35]
Body weight	87	91
Brain weight	84	87
Heart weight	84	92
Lung weight	82	84
Liver weight	82	90
Kidney weight	84	85
Placenta weight	79	69
Brain weight/ liver weight ratio	1.02	0.97

* data from original unpublished observations

As with the animal model, there is the suggestion that infants suffering combined prenatal and postnatal malnutrition, will result in a more than additive effect on the reduction of brain cell number. Infants who die of marasmus but who were of normal birth weight have a reduction of brain cell number around 15—20%. By contrast, infants who die of marasmus but who weighed less than 2000 gms at birth show a 60% reduction in cell number [61]. These data suggest that these infants were either premature and the premature is more susceptible to the effects of postnatal malnutrition or that these

infants failed to grow in utero because of maternal malnutrition and that this represents the clinical counterpart of the doubly deprived rat discussed above.

The mechanisms by which maternal undernutrition either experimentally induced or naturally occurring causes this type of fetal growth failure are poorly understood. However, studies presently underway would suggest that the transport by the placenta of certain nutrients might be impeded [40].

From a practical standpoint, the newborn with Type I IUGR usually is the product of an undernourished mother, although probably other environmental stresses will be found which produce this type of IUGR.

2.2.2 Type II IUGR

When the clinician is faced with a neonate born either at or before term who is of low birth weight for gestational age but whose head circumference and body length are near or at normal for gestational age he is most likely dealing with **the product of a vascularly deprived uterine environment** (Fig. 4). Again the data have been generated from animal models and human observations. The **animal model** most studied is the pregnant rat in which the uterine artery supplying one horn of the bicornate uterus has been ligated. This results in a reduction in blood flow to that horn which is now entirely supplied by the ovarian arteries [53]. Comparisons can then be made between fetuses in the ligated (compromised) and non-ligated (control) horn. When the ligation is performed on the 17th day of gestation certain changes are induced in both placenta and fetal organs. Placental RNase activity increases dramatically shortly after the ligation [50]. Fetal growth is retarded, but this retardation is **disproportional.** Brain weight, DNA, RNA and protein content are all normal. By contrast fetal liver shows a 40—50% reduction in weight, DNA, RNA and protein content [57]. In addition the liver is totally depleted in glycogen content [21]. Thus we have not only disproportionate growth failure but this small depleted liver has to supply glucose to a relatively large brain.

Fig. 4. Infant born at 36 weeks of gestation weighing 960 g showing clinical characteristics of IUGR Type II.

Tab. II. Effect of uterine artery ligation at day 17 in the rat and "placental insufficiency" in human fetuses at term on fetal growth and the growth of several organs; values are expressed as percent of normals.

	Rat*	Human [17]
Body weight	67	61
Brain weight	91	84**
Heart weight	84	75
Lung weight	62	62
Liver weight	62	54
Kidney weight	64	70
Placenta weight	84	—
Brain weight/ Liver weight ratio	1.47	1.56

* data from original unpublished observations

** Reduced brain weight suggests that not all the cases were typical IUGR Type II

Again whether or not a **human counterpart** of this model exists is not fully documented but certain observations suggest that it does. For example, it has been reported that infants with

IUGR have hematologic changes secondary to hypoxemia [13, 14] indirectly suggesting that vascular insufficiency may be an important factor in the etiology of some cases of IUGR (Type II). It is conceivable that in these cases **hypoxemia would have a synergistic growth retarding effect together with lack of nutrients.** There is direct evidence in human population that hypoxia will retard fetal growth [2, 26]. The IUGR found in affluent populations is more likely to be of this type (Tab. II).

Another type of infant falling into the type II category is the postmature infant. Again we have a long thin baby with a relatively normal head circumference. This type of infant can be differentiated if a careful gestational history is obtained.

2.2.3 Mechanisms of intrauterine growth retardation Type I and Type II

The mechanisms by which these two types of growth retardation are determined are yet unknown. Clearly there are two factors involved in the animal studies: **the timing of the experiments and the type of stimulus that is used.** Although the time at which the effects of maternal malnutrition begin to act upon the

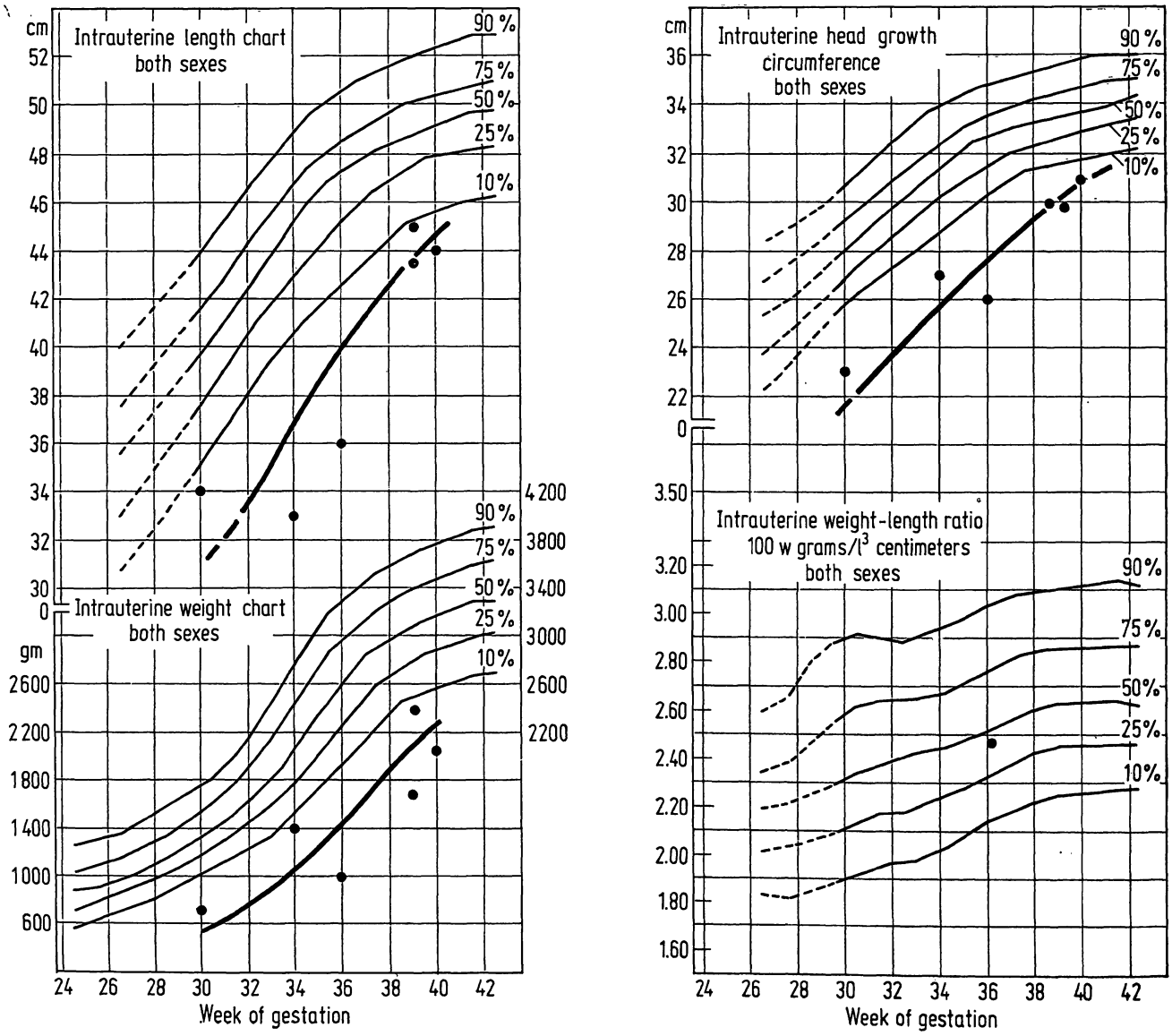

Fig. 5. Intrauterine growth of infants suffering IUGR Type I. Each point represents a separate infant whose measurements were obtained at birth [47].

placenta and the fetus is still unknown these effects probably start before day 17 of pregnancy. This assumption is based on the fact that placental DNA, which normally increases until day 17, is decreased in the malnourished rats [57]. The rate of growth of the fetal organs is different before and after day 17 [58] and consequently the effects of malnutrition, or any other factor that interferes with growth of the tissues, would also be different. This would explain why the brain, which near term is growing more slowly than liver, is spared when the uterine artery is ligated, whereas liver DNA is markedly reduced. However, what is perhaps a more plausible explanation of the disproportionate growth failure is that the **fetus near term acquires the capacity to readjust blood circulation to the different organs during periods of stress** [38]. It is likely that such mechanisms are triggered by the sudden hypoxemia induced by vascular insufficiency. Several types of evidence support this possibility [32], including experiments done in Rhesus monkeys in which vascular insufficiency, produced by ligation of the bridging vessels of the usual bidiscoid placentas, caused a marked body growth retardation without affecting the brain [20].

It has been speculated that differences in body

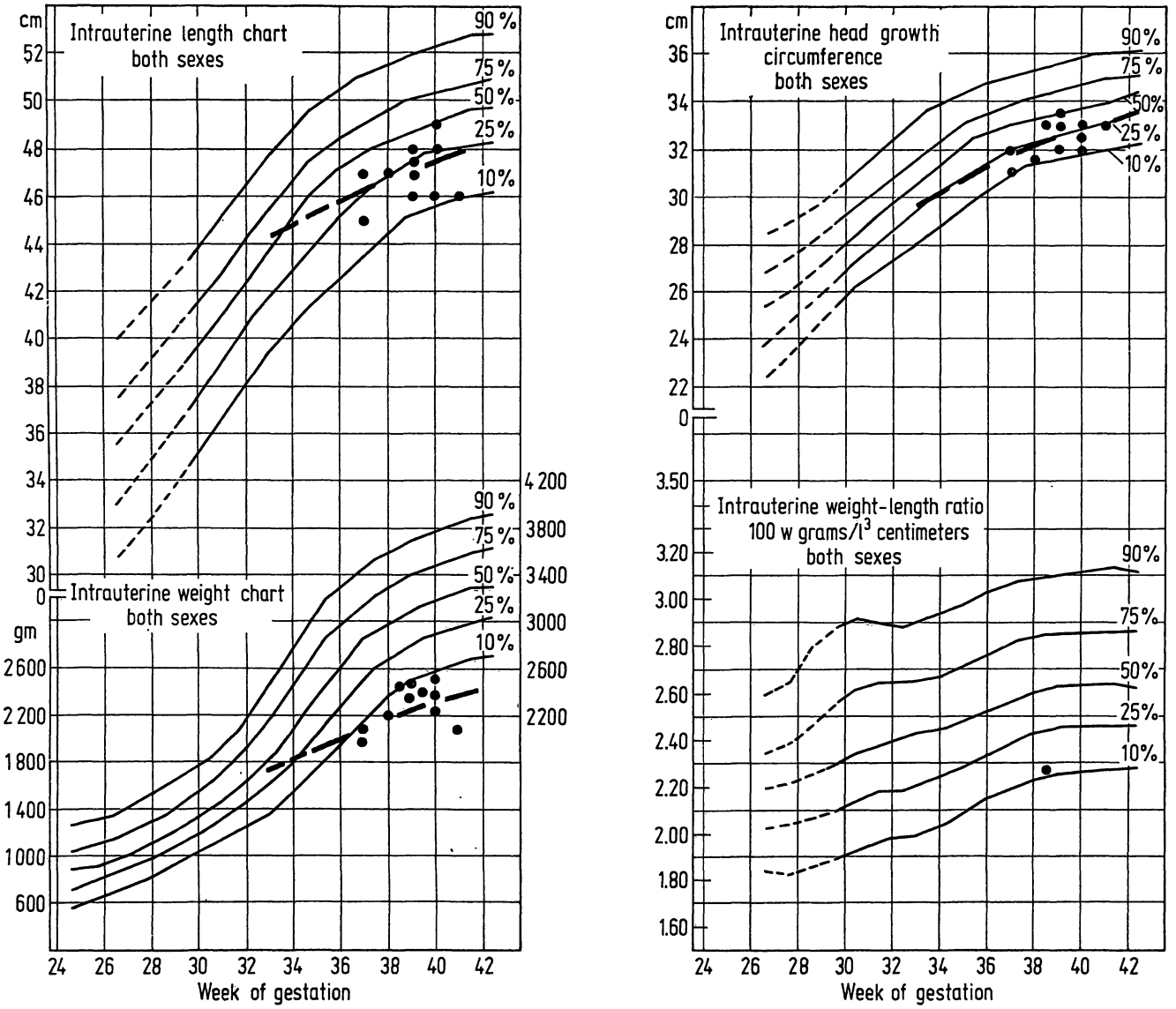

Fig. 6. Intrauterine growth of infants suffering IUGR Type II. Each point represents a separate infant whose measurements were obtained at birth [47].

proportions in the two types of human IUGR, without congenital malformations, found in human populations were also due to factors operating at different times during gestation [47]; before 28—30 weeks of gestation for Type I and 34—36 weeks of gestation for Type II (Figs. 5 and 6). However these speculations were made without any data correlating clinical types with placental growth. Since the amount of placental DNA increases in the human until 34—36 weeks [59], the placenta from Type I infants should have a marked reduction in DNA content. By contrast, placentas from Type II infants should have a normal or slightly reduced DNA content. There are data indicating that in infants with IUGR approximately 50 percent of the placental weight is above the 10th percentile [43]. This fact strongly suggests that like the infants, the **placentas may also be divided into two groups.**

It is imperative in future studies to test this possibility. It is equally important for our better understanding of the mechanisms which determine IUGR to correlate placental growth and placental histological and biochemical characteristics.

Histologically placentas from IUGR babies can be divided into two groups: those with multiple lesions and those without [24]. It would be interesting to know whether the incidence of histologic lesions differs in small and large placentas. The answer may provide new insight into the mechanisms determining the two types of IUGR.

3. Comment

This clinical classification although useful is by no means infallable. Their is a considerable overlap both in the clinical picture and also in the etiology of the types of IUGR, but this classification at least is an attempt to bring some order into the diagnosis of IUGR so that subsequent studies will be able to define exactly what type of infant they are talking about.

Infants who fail to grow in utero can be classified clinically into a number of different categories and types within those categories. Once this is done a rational approach to determining the etiology of the growth failure can be made. Now doubt, as more etiologies are uncovered and as more clinical types are recognized these classifications will need to be expanded, modified or even discarded but for the present we suggest them as an aid to obstetricians and pediatricians faced with the problem of a growth retarded infant. In addition, we suggest that researchers in describing the biochemical or physiologic changes in IUGR or the clinical characteristics and prognosis of these babies should classify them into the proper categories so that a better understanding of the particular type of infant being described is possible.

Keywords: Fetus, growth (cellular), growth disorders, newborn, placenta.

Zusammenfassung

Die intrauterine Wachstums-Retardierung
Ein neuer systematischer Vorstoß, der auf den klinischen und biochemischen Charakteristika dieses Zustandes aufbaut

Die in jüngster Zeit gewonnenen Erkenntnisse lassen vermuten, daß **Untergewichtigkeit relativ zum Gestationsalter kein einheitliches Syndrom** darstellt. In der vorliegenden Arbeit werden einige gängige Vorstellungen über die fetale Wachstums-Retardierung besprochen und neue Daten vorgelegt, die die Auffassung unterstützen, daß es zwei verschiedene, voneinander abgrenzbare Arten von intrauteriner Wachstums-Retardierung (IUGR) gibt. Die Ursachen für eine IUGR **(Fig. 1)** im Hinblick auf den Feten und die Plazenta können aufgeteilt werden in **endogen** ("intrinsic") und **exogen** ("extrinsic"). In der Gruppe der endogenen fetalen Ursachen sind die genetischen Faktoren, Chromosomenanomalien oder eine fehlerhafte Entwicklung während der Organogenese die häufigsten. Endogene plazentare Ursachen sind selten; zu ihnen gehören Plazenta-Tumoren, abnormale Nabelschnur-Insertionen und Zwillingsschwangerschaften mit Parabiose.

Die exogenen fetalen Ursachen einer IUGR wurden bisher nicht klar herausgearbeitet, wenngleich gewisse tetratogene Substanzen in diese Ursachen-Gruppe hinein gehören. Im Gegenteil, eine Vielzahl von Fällen mit

IUGR sind durch exogene Faktoren bedingt, welche Fet und Plazenta als Einheit gleichermaßen berühren. **In solchen Fällen kann der Fet nicht nur als Folge der direkten Beeinflussung durch die Substanz, sondern ebenso aufgrund der Plazenta-Beteiligung nicht regelrecht wachsen.** Die **Röteln-Infektion** ist ein Beispiel für eine solche IUGR. Die Untersuchung der Plazenten von Fällen mit kongenitaler Rubella-Infektion zeigt häufig eine villöse Plazentitis und virusbedingte Schäden der Gefäß-Endothelien. Der Herpes simplex, die Syphilis, die Malaria und die Toxoplasmose sind andere infektiöse bzw. parasitäre Erkrankungen, die mit einer IUGR einhergehen.

Es ist in einer Anzahl von Fällen mit diesen Infektions-Krankheiten schwierig, aus den verfügbaren Unterlagen zu entscheiden, ob es sich um eine Prämaturität oder um eine IUGR handelt.

Man weiß, daß **ionisierende Strahlen** eine IUGR verursachen können, wobei die IUGR mit einer schweren Schädigung des ZNS verbunden ist. Ob jedoch in diesen Fällen auch die Plazenta betroffen ist und demzufolge eine Zuteilung zu dieser Kategorie wünschenswert erscheinen läßt, geht aus den Unterlagen nicht einwandfrei hervor.

Mangelernährung der Mutter ist vermutlich eine der häufigsten Ursachen für die exogene, fetoplazentare IUGR. Über Untersuchungen bei Hungernden hinaus haben Studien in Guatemala kürzlich gezeigt, daß die zusätzliche Gabe von entweder Kalorien oder Proteinen an mutmaßlich unterernährte Mütter zu einer Zunahme des Geburtsgewichtes von ungefähr 400 g führt.

Der häufigste exogene Faktor, der vor allem die Plazenta beeinträchtigt, scheint die **Drosselung der utero-plazentaren Durchblutung** zu sein. Diese vaskuläre Insuffizienz findet ihren Niederschlag im häufigeren Vorkommen von Gefäß-Läsionen in Plazenten von Kindern mit Wachstums-Retardierung. Einige dieser Läsionen, wie z. B. blasse Bezirke, große Areale mit ischämischer Nekrose der Zotten und Infarkte findet man auch in Plazenten von normalen Neugeborenen, was darauf hinweist, daß diese Veränderungen nicht spezifisch sind.

Einige Zustandsbilder mit IUGR, die bei starken **Raucherinnen** oder bei kleinen Plazenten auftreten, sind bishier nicht klassifizierbar.

Aus **klinischer Sicht** können die in ihrem Wachstum zurückgebliebenen Neugeborenen in **zwei Hauptgruppen** eingeteilt werden **(Fig. 2)**:

Jene mit klar erkennbaren und jene ohne angeborene **Mißbildungen.** Kinder mit multiplen Geburtsfehlern können normale Plazenten haben, wie dies bei Neugeborenen mit chromosomalen oder plazentaren Abnormalitäten der Fall ist. Im letztgenannten Fall ist in der Regel eine schwere Entzündung, wie z. B. bei einer angeborenen Röteln-Infektion in der Früh-Gravidität die Ursache.

Die Gruppe ohne angeborene Mißbildungen wird von drei Typen von Kindern gebildet. Der eine Typ ist der **genetisch bedingte Kleinwuchs,** den man folglich nicht als Wachstums-Retardierung auffassen kann. Die anderen beiden Typen, die gemeinhin als **„intrauterin-mangelernährt"** angesprochen werden, können in einen Typ I und II aufgeteilt werden. **Typ I** bezeichnet ein kleines Kind mit proportioniert kleinem Kopf, reduzierter Körperlänge und verringertem Gewicht **(Fig. 3, Tab. I). Typ II** ist ein kleines Kind, dessen Kopf und Körperlänge relativ zum Gestationsalter vergleichsweise normale Masse aufweisen und dessen Quotient aus Körperlänge und Gewicht vermindert ist **(Fig. 4, Tab. II).** Beide Arten von IUGR konnten im Experiment entweder durch Einschränkung der Protein- oder der Kalorien-Zufuhr an die Mutter bzw. durch Verringerung der plazentaren Durchblutungs-Größen nachgeahmt werden. Die Ätiologie dieser beiden Arten von IUGR beim Menschen ist unbekannt, wenngleich die verfügbaren Daten vermuten lassen, daß die **mütterliche Mangel-Ernährung für Typ I und Gefäß-Faktoren für Typ II verantwortlich** sind. Obwohl die Befunde bei einer großen Anzahl von Fällen eine bestimmte Art von Wachstums-Retardierung für verschiedene Organe erkennen lassen, die mit jener im experimentellen Modell identisch ist, sind die Beweise, welche diese Schlußfolgerung stützen, indirekter Natur.

Es wird gefordert, daß zwei Faktoren bei der Ausbildung dieser beiden Arten von IUGR beteiligt sein können: Der **Zeit-Faktor** und das **Vermögen des Feten, sich auf hypoxämische Situationen einzustellen.** Die letztgenannte Möglichkeit mag erklären, warum das Gehirn bei der Gefäß-Insuffizienz oder dem Typ II nicht betroffen ist.

Obwohl diese klinische Einteilung nützlich erscheint, ist sie keinesgwgs unanfechtbar; mit ihr wurde versucht, in das Zustandsbild der IUGR etwas Ordnung zu bringen mit dem Ziel, für künftige Studien eine exakte Definition des Typus der zu untersuchenden kindlichen IUGR zu ermöglichen.

Schlüsselwörter: Fet, Neugeborenes, Plazenta, Wachstum (zelluläres), Wachstumsstörungen.

Résumé

Retardement somatique intra-utérin. Une nouvelle approche systématique basée sur les caractéristiques cliniques et biochimiques de cette condition

Les dernières observations donnent à penser que **l'insuffisance de poids du foetus par rapport à l'âge de gestation ne définit pas un seul syndrome.** Ce présent article expose diverses hypothèses relatives au retardement somatique foetal ainsi que les observations récentes sur l'existence probable de types reconnaissables différents de sujets au retardement somatique intra-utérin. (IUGR: Intrauterine growth retardation).

On peut diviser les causes de l'IUGR **(Fig. 1)** en causes

"intrinsèques" et **"extrinsèques"** au foetus et placenta. Parmi les premières, les plus fréquentes sont les facteurs génétiques, les anormalités chromosomiques ou une différenciation fautive durant l'organogénèse. Les causes "intrinsèques" placentaires sont rares et elles supposent certaines conditions telles que les tumeurs placentaires, l'insertion anormale du cordon ombilical et la gestation gémellaire parabiotique.

Les causes foetales "extrinsèques" de l'IUGR n'ont pas encore été indentifiées, bien qu'on puisse sans doute classer dans cette catégorie certains agents tératogéniques. A l'opposé, une série de cas d'IUGR sont causés par des facteurs "extrinsèques" affectant simultanément l'unité foeto-placentaire. **Ici, le foetus ne grandit pas non seulement parce qu'il est atteint directement par l'agent, mais aussi par suite de l'atteinte placentaire.** Un exemple de ce type d'IUGR est **l'infection rubéoleuse.** L'examen de placentas de cas de rubéole congénitale révèle souvent, en effet, une placentite villeuse et une lésion virale de l'endothelium vasculaire. Les autres maladies infectieuses ou parasitaires associées à l'IUGR sont le Herpes simplex, la syphilis, la malaria, la toxoplasmose. Il est toutefois difficile pour un certain nombre de ces infections de déchiffrer dans les rapports sérieux s'il s'agit de prématurité ou de retardement somatique intra-utérin.

La **radiation ionisante** est connue pour provoquer une IUGR associée à de graves lésions du système nerveux central. Quoi qu'il en soit, le placenta est aussi atteint, ce qui assure la classification dans cette catégorie même avec une documentation insuffisante.

La **malnutrition maternelle** est probablement l'une des causes les plus répandues de l'IUGR foetoplacentaire "extrinsèque". En plus des rapports relatant les famines, des études récentes effectuées au Guatemala ont illustré une augmentation de 400 g environ du poids du nouveau-né de mères présumées sous-alimentées et qui avaient reçu des suppléments de calories ou de protéines.

Les facteurs externes les plus répandus affectant en premier lieu le placenta semblent être une **réduction du flux de sang utéroplacentaire.** Cette insuffisance vasculaire se reflète dans une incidence plus élevée de lésions vasculaires trouvées dans les placentas de sujets avec retardement somatique intra-utérin. Certaines de ces lésions, telles que les aires pâles, les aires larges de nécrose ischémique de villi et les infarctus, étant aussi observées dans les placentas de nouveaux-nés normaux, elles ne peuvent donc pas être considérées comme spécifiques.

Certaines conditions, comme l'IUGR, associées à **l'usage de tabac** chez les mères ou à des petits placentas ne peuvent pas encore être classées.

Cliniquement, les nouveaux-nés avec retardement somatique intra-utérin peuvent être divisés en **deux groupes principaux (Fig. 2):** l'un avec **malformations congénitales** manifestes et l'autre sans. Les enfants souffrant de multiples défections natales peuvent avoir des placentas normaux, comme les bébés ayant des anormalités chromosomiques, ou des placentas anormaux. Dans le dernier cas, il s'agit souvent d'infections graves telles que la rubéole congénitale en début de grossesse.

Le groupe sans malformations congénitales comporte trois types d'enfants, dont l'un est le groupe des **enfants génétiquement petits,** qui ne peuvent donc pas être considérés comme somatiquement retardés. Les deux autres types, désignes communément sous la rubrique de **"maltrunition intrautérine",** peuvent être divisés en Type I et Type II. Le **Type I** est un enfant petit, dont la tête est proportionellement petite et dont la taille et le poids sont réduits **(Fig. 3, Tab. I).** Le **Type II** est un enfant petit, dont la tête et la taille sont relativement normales pour l'âge de gestation, mais dont le rapport poids/taille est réduit **(Fig. 4, Tab. II).**

Les deux types d'IUGR ont été le résultat d'exemples expérimentaux à la suite soit d'une restriction des protéines ou des calories chez la mère, soit d'une diminution du volume sanguin pénétrant le placenta. On ignore l'étiologie de ces deux types d'IUGR chez l'homme, bien qu'on soit en droit de supposer que le **Type I est la conséquence d'une malnutrition maternelle** et que, comme chez le rat, **il soit possible d'associer des facteurs vasculaires au Type II.** L'évidence appuyant cette conclusion est, néanmoins, "indirecte", bien que les données obtenues à partir d'un grand nombre de cas montrent un éventail de retardement somatique pour les divers organes qui est identique au modèle expérimental.

En postulat apparaît la possibilité de faire entrer les deux facteurs suivants dans la détermination de ces deux types d'IUGR: Le **"timing"** et la **capacité du foetus de s'adapter à l'hypoxémie.** La dernière possibilité expliquerait pourquoi le cerveau reste épargné dans l'insuffisance vasculaire ou Type II.

Cette classification clinique, bien qu'utile, n'est en aucun cas infaillible et est présentée comme une tentative pour clarifier le diagnostic de l'IUGR afin que les études subséquentes permettent de définir avec précision le type d'enfant avec IUGR soumis à examen.

Mots-clés: Croissance (cellulaire), foetus, nouveau-né, placenta, troubles de croissance.

Bibliography

[1] Aherne, W.: A weight relationship between the human foetus and placenta. Biol. Neonat. 10 (1966) 113

[2] Anderson, M., L. N. Went, J. E. Maciver, H. G. Dixon: Sickle-cell disease in pregnancy. Lancet (1960) II 516

[3] Battaglia, F.: Intrauterine growth retardation. Amer. J. Obstet. Gynec. 106 (1970) 1106

[4] Battaglia, F. C., T. M. Frazier, A. E. Hellegers: Birth weight, gestational age and pregnancy outcome with special reference to high birth weight, low gestational age in infant. Pediatrics 37 (1966) 417

[5] Bergner, L., M. W. Susser: Low birth weight and prenatal nutrition: an interpretative review. Pediatrics 46 (1970) 946
[6] Brasel, J. A., M. Winick: Maternal nutrition and prenatal growth. Arch. Dis. Child. 47 (1972) 479
[7] Brasel, J. A.: Cellular changes in intrauterine malnutrition. In: Winick, M.: Current Concepts in Nutrition II, Nutrition and Fetal Development. John Wiley, New York 1974
[8] Butler, N. R., D. G. Bonham: Perinatal mortality survey. Livingstone, Edinburgh 1963
[9] Cassady, G.: Body composition in intrauterine growth retardation. Pediat. Clin. N. Amer. 17 (1970) 79
[10] Cooper, L. Z., R. H. Green, S. Krugman, J. P. Giles, G. S. Mirick: Neonatal thrombocytopenic purpura and other manifestations of rubella contracted in utero. Amer. J. Dis. Child. 100 (1965) 416
[11] Dayton, D. H., L. J. Filer, C. Canosa: Cellular changes in the placentas of undernourished mothers in Guatemala. Fed. Proc. 28 (1969) 488
[12] Driscoll, S. G.: Histopathology of gestational rubella. Amer. J. Dis. Child. 118 (1969) 49
[13] Finne, P. H.: Erythropoyetin levels in cord blood as an indicator of intrauterine hypoxia. Acta Paediat. Scand. 55 (1966) 478
[14] Fiori, R., J. W. Scanlon: Erythrocyte levels of 2,3-diphosphoglycerate in the syndrome of fetal malnutrition. Amer. J. Obstet. Gynec. 111 (1971) 681
[15] Fujikura, T., W. H. Niemann: Birth weight, gestational age and type of delivery in Rhesus monkeys. Amer. J. Obstet. Gynec. 97 (1967) 76
[16] Gopalan, C.: Maternal and infant nutrition in underdeveloped countries. J. Amer. Diet. Ass. 39 (1961) 129
[17] Gruenwald, P.: Chronic fetal distress and placental insufficiency. Biol. Neonat. 5 (1963) 215
[18] Habicht, J. P., C. Yarbrough, A. Lechtig, R. Klein: Relationships of birth weight, maternal nutrition and infant mortality. Nutrition Rep. Inter. 7 (1973) 533
[19] Hammond, J.: Physiological factors affecting birth weight. Proc. Nutr. Soc. 2 (1944) 8
[20] Hill, D. E., R. E. Myers, A. B. Holt, R. E. Scott, D. B. Cheek: Fetal growth retardation produced by experimental placental insufficiency in the Rhesus monkey. II. Chemical composition of the brain, liver, muscle and carcass. Biol. Neonat. 19 (1971) 68
[21] Hohenauer, L., W. Oh: Body composition in experimental intrauterine growth retardation in the rat. J. of Nutr. 99 (1969) 23
[22] Hughes, W. T.: Infections and intrauterine growth retardation. Pediat. Clin. N. Amer. 17 (1970) 119
[23] Iyengar, L.: Urinary estrogen excretion in undernourished pregnant Indian women. Amer. J. Obstet. Gynec. 102 (1968) 834
[24] Laga, E. M., S. G. Driscoll, H. N. Munro: Comparison of placentas from two socioeconomic groups. I. Morphometry. Pediatrics 50 (1972) 24
[25] Laga, E. M., S. G. Driscoll, H. N. Munro: Comparison of placentas from two socioeconomic groups. II. Biochemical characteristics. Pediatrics 50 (1972) 33
[26] Lichty, J. A., R. Y. Ting, P. D. Bruns, E. Dyar: Studies of babies born at high altitude. I. Relation of altitude to birth weight. Amer. J. Dis. Child. 93 (1957) 666
[27] Longo, L. D.: Disorders of placental transfer. In: Assali, N. S., C. R. Brinkman: Pathophysiology of gestation II. Academic Press, New York 1972
[28] Lubchenko, L. O.: Assessment of gestational age and development at birth. Pediat. Clin. Amer. 17 (1970) 125
[29] Lubchenko, L. O., C. Hansman, M. Dressler, E. Boyd: Intrauterine growth as estimated from live-born birth-weight data at 24—42 weeks of gestation. Pediatrics 32 (1963) 793
[30] Mcburney, R. D.: The undernourished full term infant. West. J. Surg. Obstet. Gynecol. 55 (1947) 363
[31] Mccracken, G. H., H. R. Shinefield, K. Cobb, A. R. Ransen, R. Dische, H. F. Eichenwald: Congenital cytomegalic inclusion disease. Amer. J. Dis. Child. 117 (1969) 522
[32] Minkowsky, A., J. M. Roux, C. Tordet-Caridroit: Pathophysiologic changes in intrauterine malnutrition. In: Winick, M.: Current Concepts in Nutrition II. John Wiley, New York 1974
[33] Naeye, R. L.: Abnormalities in infants of mothers with toxemia of pregnancy. Amer. J. Obstet. Gynec. 95 (1966) 276
[34] Naeye, R. L.: Malnutrition: probable cause of fetal growth retardation. Arch. Pathol. 79 (1965) 284
[35] Naeye, R. L., W. Blanc, C. Paul: Effects of maternal malnutrition on the human fetus. Pediatrics 52 (1973) 494
[36] Peller, S.: Der Geburtstod (Mutter und Kind). Deuticke, Leipzig 1936
[37] Polani, P. E.: Chromosome anomalies. Ann. Rev. Med. 15 (1964) 93
[38] Purves, M. J., T. J. Biscode: Development of chemoreceptor activity. Brit. Med. Bull. 22 (1966) 56
[39] Reisman, L. E.: Chromosome abnormalities and intrauterine growth retardation. Pediat. Clin. N. Amer. 17 (1970) 71
[40] Rosso, P.: Maternal malnutrition and placental transfer of nutrients in the rat. Pediat. Res. 8 (1974) 359
[41] Russell, C. S., R. Taylor, C. E. Law: Smoking in pregnancy, maternal blood pressure, pregnancy outcome, baby weight and growth and other related factors. Brit. J. Prev. Soc. Med. 22 (1968) 119
[42] Scott, K. E., R. Usler: Fetal malnutrition: its incidence, causes, and effects. Amer. J. Obstet. Gynec. 94 (1966) 951
[43] Scott, J. M., J. M. Jordon: Placental insufficiency and the small-for-date baby. Amer. J. Obstet. Gynec. 113 (1972) 823
[44] Shanklin, D. R.: The influence of placental lesions on the newborn infant. Pediat. Clin. N. Amer. 17 (1970) 25

[45] Söderling, B.: Pseudoprematurity. Acta Peadiat Scand. 42 (1953) 520
[46] Sjöstedt, S., G. Engleson, G. Rooth: Dismaturity. Arch. Dis. Child. 33 (1958) 123
[47] Urrusti, J., P. Yoshida, L. Velasco, S. Frenk, A. Rosado, A. Sosa, M. Morales, T. Yoshida, J. Metcoff: Human fetal growth retardation: I. Clinical features of sample with intrauterine growth retardation. Pediatrics 50 (1972) 574
[48] van den Berg, B. J., J. Yerushalmy: The relationship of the rate of intrauterine growth of infants of low birth weight to mortality, morbidity and congenital anomalies. J. Pediat. 69 (1966) 513
[49] Vandenberg, S. G., F. Falkner: Hereditary factors in human growth. Human Biol. 37 (1965) 357
[50] Velasco, E., J. A. Brasel, D. M. Sigulem, P. Rosso, M. Winick: Effects of vascular insufficiency on placental ribonuclease activity in the rat. J. of Nutr. 103 (1973) 213
[51] Wagner, M. G.: An epidemiologic analysis of dysmaturity. Biol. Neonat. 6 (1964) 164
[52] Warkany, J., B. B. Monroe, B. S. Sutherland: Intrauterine growth retardation. Amer. J. Dis. Child. 102 (1961) 249
[53] Wigglesworth, J. S.: Experimental growth retardation in the fetal rat. J. Pathol. Bacter. 88 (1964) 1
[54] Winick, M., E. Velasco, P. Rosso: DNA content of placental and fetal brain. Pan. Am. Health Org. Scient. Publ. 185 (1969) 531
[55] Winick, M., A. Noble: Cellular response in rats during malnutrition at various ages. J. Nutr. 89 (1966) 300
[56] Winick, M.: Cellular growth of human placenta. III. Intrauterine growth failure. J. of Pediatrics 71 (1967) 390
[57] Winick, M.: Cellular growth of the placenta as an indicator of abnormal fetal growth. In: Adamsons, K.: Diagnosis and treatment of fetal disorders. Springer, New York 1969
[58] Winick, M., A. Noble: Quantitative changes in DNA, RNA and protein during prenatal and postnatal growth in the rat. Develop Biol. 12 (1965) 451
[59] Winick, M., A. Coscia, A. Noble: Cellular growth in human placenta I. Normal placental growth. Pediatrics 39 (1967) 248
[60] Winick, M., J. A. Brasel and P. Rosso: Nutrition and cell growth. In: Winick, M.: Nutrition and Development. John Wiley, New York 1972
[61] Winick, M., P. Rosso: The effects of severe early malnutrition on cellular growth of human brain. Pediat. Res. 3 (1969) 181
[62] Wong, T. C., J. P. A. Latour: Microscopy measurement of the placental components in an attempt to assess the malnourished new born infant. Amer. J. Obstet. Gynec. 94 (1966) 942
[63] Yamazaki, J.: A review of the literature on the radiation dosage required to cause manifest central nervous system disturbances from "in utero" and postnatal exposure. Pediatrics 37 (1966) 877
[64] Younouszai, M. K., J. C. Haworth: Placental dimensions and relations in preterm, term and growth retarded infants. Amer. J. Obstet. Gynec. 103 (1969) 265

Dr. Pedro Rosso
Institute of Human Nutrition
College of Physicians and Surgeons
Columbia University
630 West 168th Street
New York, N. Y. 10032/USA